56. The method of claim 34 wherein administering the prolactin enhancer adjusts the daily prolactin peak of the tumor bearing mammal to peak at night.

REMARKS

I. Claim Amendment. Amended claim 8 is drawn to an embodiment of the invention wherein a tumor bearing mammal is subjected to the combination of neuroendocrine rhythm resetting therapy and PDT. Support for the amended claim is found throughout the specification, e.g., at page 10, lines 1-7; page 14, lines 20-15; and page 16, lines 15-22.

New claims 55 and 56, directed to adjusting peak prolactin levels, are supported in the specification at page 3, lines 3-6; page 13, lines 24-27; page 14, lines 16-18; and page 15, lines 26-29.

As the amendment and new claims are supported in the specification, no new matter has been introduced into the application.

II. Claim Status. By this amendment, claims 34-47 and 49-56 are pending in the application.

III. Claim Rejections. The rejections are summarized and addressed as follows.

(i) Double patenting rejections. Claims 34-35, 43 and 49 have been rejected for obviousness-type double patenting over claim 18 of U.S. Patent No. 6,071,914 ("the '914 patent") in view of Cincotta et al. (Cancer Res., 1994, 54:1249-1258) and Lin (Cancer Cells, 1991, 3:437-444). The instant rejection depends on the Examiner's assertion that the '914 patent claims a method for arresting the growth of, or eradicating, tumors by adjusting the prolactin rhythm profile of a tumor bearing mammal, by administering a prolactin reducer, as recited in the instant

claims. In response, without prejudice or disclaimer, the amended claims have been limited to methods of treatment in which the prolactin rhythm profile of a tumor bearing is adjusted with a prolactin enhancer. The '914 fails to claim any method in which the prolactin rhythm profile of a tumor bearing mammal is adjusted with a prolactin enhancer. Nor is a method of resetting the prolactin rhythm profile of a tumor bearing with a prolactin enhancer obvious from the claims of the '914 patent. Hence, the rejections are addressed and overcome. Accordingly, applicants respectfully request reconsideration of claims 34-35, 43 and 49 and withdrawal of all obviousness-type double patent rejections based on U.S. Patent No. 6,071,914.

Claims 34-36, 39, 43 and 49 have been rejected for obviousness-type double patenting over claims 3, 8 and 13 of U.S. Patent No. 5,792,748 ("the '748 patent") in view of Werning et al. (Arch. Ontolaryngol. Head Neck Surg., 1995, 121:783-789), Cincotta et al. (Cancer Res., 1994, 54:1249-1258) and Molitch (Endocrinol. Metab. Clin. North Am., 1992, 21:877-901 ABSTRACT ONLY). Applicants respectfully traverse. The references cited by the Examiner do not, neither individually nor in combination, suggest treating tumors with the combination of neuroendocrine resetting therapy and PDT.

The '748 patent discloses and claims methods of inhibiting neoplastic growth in a mammal using neuroendocrine resetting therapy with prolactin. The '748 patent does not contain any teaching or suggestion that neuroendocrine resetting therapy using a prolactin enhancer should be used in combination with PDT to arrest or eradicate tumors in a mammal, as presently claimed. There is no hint in the patent that any benefit would be achieved with such a combination. Rather, the '748 patent is silent as to combining neuroendocrine resetting with any other treatment, including PDT. The '748 patent therefore fails to suggest that neuroendocrine

resetting therapy be combined with PDT to arrive at the instantly claimed invention.

The Examiner attempts to cure the defect of the '748 patent with Werning et al. But Werning et al. also contains no disclosure or suggestion that a tumor bearing mammal be treated with the combination of PDT and neuroendocrine resetting therapy. Werning et al. disclose, at most, administering metoclopramide at particular time points relative to PDT (i.e., 1h before and 24 and 48 h after PDT; see Werning et al., page 785, "PDT PLUS METOCLOPRAMIDE"). This type of administration is not remotely equivalent to the administration regime required to reset the daily prolactin rhythm.

Nor do Werning et al. suggest administering a prolactin enhancer to reset a daily prolactin rhythm. Werning et al. teach that the benefit of combining metoclopramide administration with PDT is derived from metoclopramide's direct enhancement of PDT, through enhancement of DNA damage or increased blood flow and oxygen availability to the tumor (see Werning et al., page 787, bottom of column 1 and page 788, column 2.) They make no suggestion that these, or any other effects derived from metoclopramide administration, would be enhanced by using metoclopramide (or any other prolactin enhancer) to reset the daily prolactin rhythm. Rather, Werning et al. are silent as to the presence of prolactin daily rhythm in a mammal. Accordingly, Werning et al. fail to disclose any benefit or advantage of combining PDT with the step of administering a prolactin enhancer to adjust the daily plasma prolactin profile of a tumor bearing mammal to conform to or approach the normal daily plasma prolactin profile for healthy members of the same species and sex of the mammal, as recited in the instant claims. Hence, Werning et al. fail to provide any motivation or suggestion of success for treating tumors with the combination of neuroendocrine resetting therapy and PDT, as claimed.

The Examiner bears the burden of establishing a prima facie case of obviousness based upon the prior art. Both the suggestion of making the present invention, and a reasonable expectation of success must be founded in the prior art, not in Applicants' disclosure. *In re Dow Chemical Co.*, 837 F.2d 469, 5 USPQ2d 1529, 1531 (Fed. Cir.1988). Contrary to the Examiner's assertion, however, neither the '748 patent, nor Werning et al., neither alone nor in combination, contain the required suggestion to treat tumors by combining neuroendocrine resetting therapy and PDT. Accordingly, Applicants respectfully suggest that the Examiner has relied on and applied an obvious to try standard as the rationale for combining the cited references to arrive at the presently claimed invention. Obvious to try is not a valid test of patentablility. *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q.2d 1529, 1531 (Fed. Cir.1988); *In re O'Farrell,* 853 F.2d 894, 7 U.S.P.Q.2d 1673 (Fed. Cir. 1988); *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 U.S.P.Q. 81 (Fed. Cir.1986); *In re Geiger,* 815 F.2d 686, 2 U.S.P.Q.2d 1276 (Fed. Cir. 1987). Hence, the present rejections should be removed.

Objective Evidence of Non-obviousness

Applicants further traverse the obviousness-type double patenting rejections on the grounds that treating tumors with the combination of neuroendocrine resetting therapy and PDT leads to unexpected results, compared to the results obtained when each method is used alone. These results are objective evidence that the claimed methods are non-obvious.

The unexpected results obtained by treating tumors with the combination of neuroendocrine resetting therapy using a prolactin enhancer and PDT are set forth in Examples 1-3 of the specification. Example 1 (at page 28) describes an experiment designed to measure the effect of control (C), prolactin (PRL; 20 mcg/mouse at 10 h after light onset at 7 days after tumor

inoculation, continuing for 14 days), PDT (D + L; EtNBS photosensitizer; power density of 100J/cm^2 and a total energy of 100J/cm^2) and prolactin plus PDT (D + L + PRL) treatments on tumors in mice. The results of the experiment that are shown in Figure 5 demonstrate the unexpected synergistic effect of the combined treatment.

As shown in Figure 5, the average tumor volume of animals treated with prolactin alone was found to be 56% of the average tumor volume of control animals (i.e., prolactin treatment reduced average tumor volume by 44%). The average tumor volume of animals treated with PDT alone was 43% of the average tumor volume from control animals (i.e., PDT reduced average tumor volume by 57%.) Based on these results, therefore, the average tumor volume in animals treated with both prolactin and PDT, obtained by multiplying the results of each individual treatment (i.e., 0.56 x 0.43), is predicted to be 24% of the average tumor volume of control animals (i.e., 76% reduction in the average tumor volume compared to control cells.)

The results given in Figure 5 demonstrate, however, that actual combined treatment with prolactin and PDT is more effective than the results predicted from each treatment alone. Hence, the combined treatment actually reduced average tumor volume by 92.4%, compared to control animals, and compared to the predicted value of 76% for the combined treatment. Stated differently, the results showed that the average tumor volume of animals that received the combined treatment was only 7.6% the average tumor volume of control animals. This value is over 3-fold lower than the value of 24% predicted for the combined treatment, based on the results of the individual treatments. Hence, the combined treatment with PDT and prolactin lead to an unexpectedly greater reduction in tumor volume than that predicted from the results obtained with each treatment alone. The results of Example 1 are therefore objective

evidence of the non-obviousness of the combined treatment over either treatment alone.

Further experimental evidence of the unexpected synergy obtained in treating tumors with combined neuroendocrine resetting therapy with a prolactin enhancer and PDT is set forth in Example 2 (pages 28-30). Example 2 reports that, when PDT with the benzophenothiazine photosensitizer EtNBS is used alone, at a power density of 50 mW/cm^2 and a total energy of 180 J, tumor "cure" (tumor-free for at least 90 days) of 4-8 mm diameter tumors can be achieved in 70-100% of the cases, and is largely dependent upon the tumor size at the time of PDT. In contrast, if intraperitoneal prolactin is administered (20 mcg/mouse/day at 10 h after light onset, starting from day of tumor cell inoculation) in conjunction with PDT, then the cure rate is 100%. (Though not reported in the examples, many previous experiments have shown that neuroendocrine resetting therapy alone does not lead to a significant cure rate, as defined above.) Furthermore, the time course of tumor eradication is significantly faster with the combined treatment versus PDT alone. Hence, tumors remained noticeable 48-72 h following PDT treatment alone, taking 14 days to regress completely, with eschar formation at 24-48 hours. In contrast, when timed administration of prolactin was combined with PDT, 100% of the treated animals exhibited eschar formation and complete tumor eradication within 24 h of PDT. Hence, in Example 2, the combination of neuroendocrine resetting therapy and PDT lead to more rapid tumor eradication and a higher tumor eradication rate (i.e., 100%), compared to PDT alone.

These results were confirmed in Example 3 (pages 29-30), using different PDT parameters, i.e., the benzophenothiazine photosensitizer Dye 4-115, at a power density of 50 mW/cm^2 and a total energy of 100 J/cm^2. Animals receiving PDT alone exhibited eschar formation at 24-48 hours. Noticeable tumor remained at 48-72 h, and took 14 days to regress

completely. In contrast, 100% of animals receiving combined neuroendocrine resetting therapy (20 mcg/mouse at 10 hours after light onset, starting 7 days after tumor inoculation and continuing for 14 days) and PDT exhibited severe eschar formation and complete tumor regression within 24 h of PDT. Hence, under these conditions, the combination of neuroendocrine resetting therapy and PDT lead to a more rapid rate of tumor eradication and a higher cure rate (of 100%), compared to PDT alone.

In summary, the results of three independent experiments demonstrate the unexpected efficacy that is achieved by combining neuroendocrine resetting therapy with a prolactin enhancer and PDT, as claimed.

In light of the forgoing remarks, Applicants respectfully submit that claims 34-36, 39, 43 and 49 are not obvious over claims 3, 8 and 13 of U.S. Patent No. 5,792,748 in view of Werning et al., Cincotta et al. and Molitch. Accordingly, Applicants respectfully request reconsideration of claims 32-36, 39, 43 and 49 and withdrawal of all obviousness-type double patenting rejections of the claims over the combination of U.S. Patent No. 5,792,748, Werning et al., Cincotta et al. and Molitch.

(ii) Claims rejected under 37 C.F.R. § 103 (a). Claims 34-47 and 49-54 are rejected as obvious over U.S. Patent Nos. 5,792,748 and/or 6,071,914 in view of Werning et al., Cincotta et al., and Molitch.

Applicants respectfully traverse the obviousness rejections on the same grounds set forth above in regard to the obviousness-type double patenting rejections. The references cited by the Examiner do not, neither individually nor in combination, suggest treating tumors with the combination of neuroendocrine resetting therapy using a prolactin enhancer and PDT.

Briefly, as set forth above, the '748 patent does not teach or suggest that neuroendocrine resetting therapy using a prolactin enhancer be used in combination with PDT to arrest or eradicate tumors in a mammal, as claimed. Nor does the '914 patent, which is division of the '748 patent. The patents are silent and afford no hint for combining neuroendocrine resetting with any other treatment, including PDT. They fail to suggest that neuroendocrine resetting therapy can or should be combined with PDT to arrive at the instantly claimed invention, or that any particular benefit or result would be achieved with such a combination.

Nor is the defect in the '748 and '914 patent cured by the teachings of Werning et al., as asserted by the Examiner. Werning et al. do not disclose or suggest that a tumor bearing mammal can or should be treated with the combination of PDT and neuroendocrine resetting therapy. Werning et al. are silent as to the presence of a prolactin daily rhythm in a mammal. Accordingly, Werning et al. fail to disclose any benefit or advantage of combining PDT with the step of administering a prolactin enhancer to adjust the daily plasma prolactin profile of a tumor bearing mammal to conform to or approach the normal daily plasma prolactin profile for healthy members of the same species and sex of the mammal, as recited in the instant claims.

Applicants respectfully suggest again that the Examiner has applied an obvious to try standard as the rationale for combining the cited references to arrive at the presently claimed invention. Obvious to try is not a valid test of patentablility.

In further support of the non-obviousness of the present claims, the Examiner's attention is again drawn to the unexpected results obtained when treating tumors with combined neuroendocrine resetting therapy using a prolactin enhancer and PDT is compared to treatment with either procedure standing alone. As set forth in Examples 1-3 and Figure 5 of the present

specification, and as discussed at length above, the combined treatment gives synergistic results that are not predicted from the individual treatments. These unexpected results are objective evidence that the present claims are not obvious.

For the reasons set forth above, Applicants respectfully suggest that claims 34-47 and 49-54 are not obvious from the combination of U.S. Patent Nos. 5,792,748 and/or 6,071,914 in view of Werning et al., Cincotta et al., and Molitch. Accordingly, Applicants respectfully request reconsideration of claims 34-47 and 49-54 and withdrawal of all rejections under 35 U.S.C. § 103 (a).

IV. Ownership/Inventorship of U.S. Patent Nos. 5,792,748 and 6,071,914.

The Examiner has asked for clarification of the ownership and inventorship of U.S. Patent Nos. 5,792,748 and 6,071,914. U.S. Patent No. 5,792,748 is owned by The General Hospital Corporation and The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College. The named inventors, Anthony H. Cincotta and Albert H. Meier are joint inventors for each of the claims in the '748 patent. U.S. Patent No. 6,071,914 is owned by Ergo Science Incorporated and The Board of Supervisors of Louisiana State University and Agricultural and Mechanical College. Anthony H. Cincotta and Albert H. Meier are also joint inventors of each claim in the '914 patent. The present application is owned by The General Hospital and the Rowland Institute for Science. The named inventors, Anthony H. Cincotta and Louis Cincotta are joint inventors of each pending claim of the present application.

Applicants respectfully submit that the non-obviousness of the instant claims over the prior art of record renders further inquiry into inventorship and ownership of the instant invention and the invention claimed in the '748 and '914 patents moot. Should the Examiner

wish further information regarding these issues, however, he is requested to contact Applicant's agent at the number listed below.

CONCLUSION

Therefore, in view of the above amendments and remarks, it is respectfully requested that the application be reconsidered and that all pending claims be allowed and the case passed to issue.

If there are any other issues remaining which the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the telephone number indicated below.

Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Anthony H. CINCOTTA; Louis CINCOTTA

Serial No.: 09/187,768 Art Unit: 1642

Confirmation No.: 3476

Filed: November 6, 1998 Examiner: G. Nickol

For: **GROWTH INHIBITION AND ERADICATION OF SOLID TUMORS USING NEUROENDOCRINE RESETTING THERAPY AND PHOTODYNAMIC THERAPY**

MARK-UP TO AMENDMENT UNDER 37 C.F.R. 1.121

U.S. Patent and Trademark Office
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December 14, 2001

Sir:

Pursuant to 37 C.F.R. § 1.121, the accompanying Amendment amends the subject application, as follows:

EXPRESS MAIL CERTIFICATE
Date 12/14/01 Label No. EL 767720710-US
I hereby certify that, on the date indicated above, this paper or fee was deposited with the U.S. Postal Service & that it was addressed for delivery to the Assistant Commissioner for Patents, Washington, DC 20231 by "Express Mail Post Office to Addressee" service.

B.W. LEE Name (Print) B.W. Lee Signature

IN THE CLAIMS

Claims 55 and 56 have been added.

Claim 34 has been amended as follows:

34. (Twice amended) A method for arresting the growth of or eradicating tumors in a mammal bearing one or more tumors comprising the steps of:

(a) comparing the daily plasma prolactin profile of said tumor bearing mammal to a normal daily prolactin profile for healthy mammals of the same species and sex;

(b) adjusting the daily plasma prolactin profile of said tumor bearing mammal by administering a prolactin enhancer [or prolactin inhibitor] at appropriate time intervals of day such that the adjusted daily plasma prolactin profile of said tumor bearing mammal conforms to or approaches the normal daily plasma prolactin profile for healthy members of the same species and sex of said mammal;

(c) contacting the cells of said tumor with a benzophenoxazine-analog photosensitizer having phototoxicity against tumor cells; and

(d) exposing said contacted tumor cells to light, such that the growth of said tumor is retarded or said tumor is eradicated.

Negative person must cancel ODP.